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Development and simulation of deactivation process of favipiravir in a pharmaceutical wastewater system

Kananan Thongsubsai[1], Sitthinon Ousamanee[2], Jindarat Pimsamarn[1], and Kantharakorn Macharoen[1]*

[1] Department of Chemical Engineering, Faculty of Engineering, King Mongkut's University of Technology Thonburi, Bangkok 10140, Thailand
[2] Chulabhorn Royal Pharmaceutical Manufacturing Facility, Chon Buri 20180, Thailand

***Corresponding author**:
Kantharakorn Macharoen
kantharakorn.mac@mail.kmutt.ac.th

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ABSTRACT

Favipiravir (FPV) has been widely used to treat COVID-19 patients in many countries, including Thailand, owing to its potent antiviral activity. Consequently, the wastewater discharged from the formulation process contains a significant amount of active pharmaceutical ingredients that could be harmful to humans and animals if released into the environment without proper treatment. Therefore, this study aimed to develop a deactivation process for FPV present in wastewater using SuperPro Designer Version 10 program. The deactivation processes were classified as two cases: case I (base case) using sodium hypochlorite (NaOCl) at 10% v/v and case II using ozone at 16 g/L. Each case was separated into a subcase A, representing the lack of a filtration unit, and subcase B, representing the use of a filtration unit. The operations used in this study can be characterized as the deactivation unit, neutralization unit, and filtration unit, selected from the equipment available at CRPMF. The simulation results showed that case IIA (with ozone and without filtration) provided the greatest deactivation of FPV per year (65,661 kg/year) but required higher annual investment and operating costs. Meanwhile, case IA (with NaOCl and without filtration) demonstrated an FPV deactivation of 49,243 kg per year, with a cost seven times lower than that of case IIA. In summary, the simulation and cost analysis information were provided to assist CRPMF and other pharmaceutical manufacturers in selecting the scenario that is best suited for the annual capacity of antiviral drug formulation.

Keywords: chemical deactivation; favipiravir; pharmaceutical manufacturing; simulation; technoeconomic

1. INTRODUCTION

The pharmaceutical industry has always served as one of the most important industries because of the continuous demand for medication to treat a variety of diseases. Although these drugs can treat various diseases and enhance the quality of life, it is important to consider the environmental impact of the wastewater produced during the manufacturing of these drugs. The presence of pharmaceutical compounds in wastewater is considered a significant ecological issue (Morales-Paredes et al., 2022). Typically, active pharmaceutical ingredients (APIs) are present in wastewater and surface waters from wastewater outlets at concentrations between the pg/L and g/L levels (Antoniou, et al., 2013). However, even at low concentrations, the chronic exposure of APIs to people and wildlife is a concern for science and society (Antoniou, et al., 2013).

Favipiravir (FPV) serves as a competitive RNA-dependent polymerase inhibitor. FPV is a purine nucleoside analog used to treat viral hemorrhagic fever and influenza types A and B (Tulbah and Lee, 2021). In 2014, the Japan Pharmaceuticals and Medical Devices Agency approved FPV for the treatment of pandemic influenza strains under the AVIGAN® brand, owing to its well-established safety profile (Tulbah and Lee, 2021; Manabe et al., 2021). FPV has also been used for the treatment of COVID-19 in some countries, likely owing to its ability to inhibit viral replication and transcription. A study by Jin et al. (2013) demonstrated that FPV incorporates itself with the influenza virus, inhibiting the further expansion of the virus (Jin et al., 2013). During the influenza epidemic in Japan, Azuma et al. (2013, 2017) found that the FPV concentration detected in the surface waters of effluents from wastewater treatment plants ranged from 40–60 ng/L (Azuma et al., 2013, 2017). Some antiviral drugs are known to be highly bioactive and lead to the resistance of non-target organisms in aquatic ecosystems (Nippes et al., 2021). Therefore, highly efficient wastewater treatment plants are needed to deactivate the antiviral drugs present in the wastewater.

Sodium hypochlorite (NaOCl) is an oxidizing agent that can react with a wide range of compounds, including organic compounds, inorganic compounds, and metal ions. When NaOCl reacts with compounds containing double bonds, a chlorine atom can be added across the double bond, known as electrophilic substitution. In addition, NaOCl reacts with organic compounds containing functional groups such as alcohols, amines, and amides (Wang, 2010). Our recent study found that 0.01 M NaOCl demonstrates considerable deactivation of 1 mg/mL of FPV. According to the manufacturer of the FPV active ingredient, a 10% v/v solution should effectively deactivate the residual FPV in a wastewater system.

Ozone (O_3) is a highly reactive molecule that can react with a wide range of organic compounds, containing functional groups such as double bonds, triple bonds, and aromatic rings. An oxygen atom is added across the double or triple bond, known as electrophilic addition, when O_3 reacts with unsaturated hydrocarbons (Vogna et al., 2004). O_3 can also react with aromatic compounds, such as aromatic hydrocarbons and heterocyclic compounds, in which an oxygen atom is added to the aromatic ring, known as ozonolysis (Vogna et al., 2004). Additionally, O_3 does not produce toxins after treatment and can precipitate suspended solids, resulting in a decrease in turbidity (Chayliem, 2018). In this study, O_3 was selected for the FPV deactivation reaction owing to its high reactivity and low footprint.

The removal of various harmful pollutants through the use of conventional industrial wastewater treatment processes such as precipitation, absorption, oxidation, and filtration has been well-established; however, these techniques have limitations. They may not entirely remove all contaminants from the water, leaving behind residual pollutants and emerging contaminants such as pharmaceuticals and microplastics, which mitigates the effectiveness of such methods (Singh and Singh, 2019). As chemical treatment is an effective method for the deactivation of drugs, this study utilized this strategy to deactivate FPV. NaOCl and O_3 were used to oxidize FPV, as they are strong oxidizing agents. The SuperPro Designer V.10 simulation program was used to develop and simulate the chemical deactivation processes of wastewater systems (e.g., Chulabhorn Royal Pharmaceutical Manufacturing Facility [CRPMF]) containing FPV. The program facilitates the modeling, evaluation, and optimization of batch and continuous processes integrated over a wide range of industries, such as biotechnology, pharmaceuticals, food processing, wastewater treatment, and air pollution control.

2. MATERIALS AND METHODS

2.1 Process description

The process of FPV deactivation in the pharmaceutical wastewater system proposed in this study consists of three components, as shown in Figure 1. The first component is the deactivation unit, performing the deactivation of FPV presented through the production process. The next component is the filtration unit, which removes suspended particles from the wastewater. Finally, the last component is the neutralization unit, which adjusts the pH value to be suitable for release into the environment or for further treatment. This process is based on the equipment available at CRPMF.

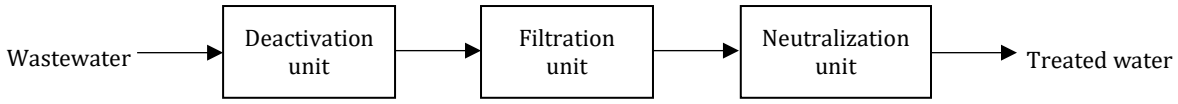

Figure 1. Operation of the deactivation process available at CRPMF

The FPV deactivation process was examined by considering two different cases, designed and simulated in SuperPro Designer V.10. In general, FPV is dispersed in water as a fine suspension, depending on its concentration. As such, each considered case contains subcases A and B, which represent the disregard (low FPV drug concentration and fine suspension) and consideration (high FPV drug concentration and fine-to-moderate suspended mixture) of the filtration unit, respectively, providing alternative conditions and operations for the wastewater plant.

2.1.1 Case I scenario

As shown in Figure 2, the case I scenario (base case of CRPMF operation) used NaOCl at an initial concentration of 10% v/v as a deactivating agent and was separated into two subcases—case IA without filtration and case IB with the filtration unit implemented.

2.1.2 Case II scenario

Like the case I scenario, the case II scenario was separated into two subcases—with and without filtration—as shown in Figure 3. As case II involve the use of O_3 as a deactivating

agent at an initial concentration of 16 g/L, an O_3 generator was required in this case.

2.2 Process assumption

It is necessary to obtain information or formulate assumption that the program needs to simulate the process. In this study, the following assumptions were made:

- The amount of wastewater was assumed to be 2,500 L per batch, according to information acquired from CRPMF.
- The wastewater of CRPMF was presumed to contain 0.5% w/v of FPV and 0.09% w/v of other insoluble excipients, such as low-substituted hydroxypropyl cellulose (L-HPC LH-11), colloidal silicon dioxide, crospovidone, and sodium stearyl formulate.
- Sulfuric acid (H_2SO_4) at 0.0019% w/w was added to represent the acidity of the wastewater (pH 3.7).
- The ratio of wastewater to NaOCl solution (10% v/v, 249 kg/batch) was 10:1, according to information provided by the manufacturer.
- Sodium hydroxide (NaOH) at 0.0021% w/w was added to represent the basicity of NaOCl (pH 11).
- The deactivation reaction of FPV with NaOCl was assumed by the mass stoichiometry in Equation (1) (Vogna et al., 2004; Chitniratna and Peungsangarunchai, 2021).
- Conversion through the deactivation reaction between NaOCl and FPV in the wastewater was assumed to take place at 99%, per the manufacturer's recommendation for a complete reaction time of 30 min (Chitniratna and Peungsangarunchai, 2021).
- O_3 at 16 g/L (20 kg/batch) was assumed to sufficiently deactivate 5 g/L of FPV (Antoniou et al., 2013; Chayliem, 2018).
- The deactivation reaction of FPV with O_3 was assumed by the mass stoichiometry in Equation (2) (Chayliem, 2018).
- Conversion through the above reaction was assumed to take place at 99% (Antoniou et al., 2013), with a reaction time of 30 min (Chayliem 2018; Huber et al., 2003). Neutralization was assumed to take 30 min to proceed (Jarnerud et al., 2021).
- Neutralization reactions were represented by the molar stoichiometry in Equation (3).

$$157.10\ \text{FPV} + 74.44\ \text{NaOCl} \rightarrow 173.10\ \text{Deactivated FPV} + 58.44\ \text{NaCl} \quad (1)$$

$$157.10\ \text{FPV} + 48\ O_3 \rightarrow 173.10\ \text{Deactivated FPV} + 32\ O_2 \quad (2)$$

$$2\ \text{NaOH} + H_2SO_4 \rightarrow Na_2SO_4 + 2\ H_2O \quad (3)$$

- Conversion through the neutralization reaction was assumed to be 100%.
- The press and frame filtration was assumed to take 30 min to remove the solid particles suspended in the wastewater with an efficiency of 98%, according to the CRPMF Filter Manual (Piemont et al., 2021).
- An adiabatic process, set as the default mode in the software, was assumed for each unit operation. Temperature changes were assumed to be negligible.

3. RESULTS AND DISCUSSION

3.1 Simulation results

The processes of FPV deactivation in case I without and with a filtration unit are shown in Figures 2a and 2b, respectively, while the alternative subcases (case II) are shown in Figure 3a (without filtration) and Figure 3b (with filtration). The focus in this study, was the deactivation, neutralization, and filtration processes only. After this set of processes, the effluent wastewater was transferred to the activated sludge unit for further treatment. The details of each unit are discussed below.

3.1.1 Deactivation unit

Approximately 2,500 L (~2,488 kg) of wastewater generated from cleaning and washing the formulation equipment was transferred to the deactivation tank (S-102), as illustrated in Figures 2a and 2b for case I. The wastewater contained 0.5% w/v (5 g/L) of FPV and insoluble excipients. Afterward, 250 L of 10% v/v (111.4 g/L) NaOCl (S-101) was added to the deactivation tank. The reaction time was set at 30 min in a 25-m^3 deactivation tank (P-1 / R-101). For simulation purposes, the wastewater feed line (S-102) and NaOCl feed line (S-101) were supplied with 0.01891 g/L H_2SO_4 to represent the acidity in the wastewater (pH 3.7) and 0.02089 g/L NaOH to represent the basicity of the NaOCl solution (pH 11), respectively. However, in practice, the two reagents are not added to the deactivation tank. The effluent of the deactivation tank (S-104) contained 0.05 g/L of FPV, corresponding to 99% deactivation as expected. Actual experiments were required to support this assumption.

Figures 3a and 3b show that the FPV wastewater (5 g FPV/L) was mixed with compressed O_3 gas (16 g/L) from the O_3 generator (P-1 / PFR-101) in the mixer (P-2 / MX-101) before feeding to the deactivation tank (P-3 / R-101). H_2SO_4 was added to the wastewater streamline as mentioned above, while O_2 gas was used to generate O_3 gas in the PFR-101. At the mixer, FPV immediately reacted with the O_3 solution, producing 0.98 g FPV/L, which entered the deactivation tank. As in case I, the FPV concentration in the effluent of the deactivation tank was 0.05 g/L corresponding to 99% deactivation, as assumed after 30 min of reaction time.

Figures 2a and 3a show that 2,736 kg and 2,489 kg of effluent, respectively, containing suspended particles, were directly transferred to the neutralization tanks without occupying the filtration unit. The use of O_3 as a deactivating agent in case IIA was found to not significantly increase the weight of the corresponding effluent, whereas the NaOCl treatment in case IA did significantly increase the weight of the corresponding effluent. Although installing an O_3 generator in case II increased the number of treatment batches of case IIA (Table 1), which could de-bottleneck the production capacity, it also increased the overall cost (Table 2). The treatment of FPV wastewater with O_3 is an attractive choice because it can oxidize and deactivate a large collection of organic compounds and enhance the biodegradability of the wastewater (Hussain, et al., 2020).

3.1.2 Filtration unit

Filtration might be required in the FPV deactivation process, depending on the size and load of the suspended particles from the FPV drug excipients. Figures 2b and 3b show that the filtration units received the underflow effluents from the deactivation unit at 271 kg per batch (S-103) in case IB and 249 kg per batch (S-105) in case IIB, respectively, assuming 98% efficiency (Piemont et al., 2021). A split command in the program was used to separate the precipitated solids from the deactivation tank and transfer them to the filtration unit. Assuming a negligible amount of coagulant was added to the deactivation tank, solid particles including colloidal silicon dioxide (density of 2.65 g/cm^3), crospovidone (density of 1.2 g/cm^3), L-HPC LH-11 (density of 1.3 g/cm^3), and sodium stearyl fumarate (density of 1.107 g/cm^3) were agglomerated and precipitated. The precipitated particles were then transferred to the plate and frame filtration unit with a cross-sectional area of 1.3 m^2 and operation time of 30 min. The wet cakes in case IB and case IIB were both 2.96 kg per batch. In general, the wet cake is removed and dried before cake incineration and sludge cake treatment (Ki et al., 2021). The rest was filtrate that was to be transferred for further treatment, such as that provided by the neutralization unit.

As expected, incorporating the filtration unit into the wastewater treatment resulted in a decrease in the number of operation batches per year (Table 1) and an increase in the overall costs (Table 2) for both case I and case II. Although plate and frame filtration is commonly used for sludge dewatering (Zhang et al., 2022), employing filtration after the FPV deactivation unit may not be necessary if the suspended particles are fine and diluted.

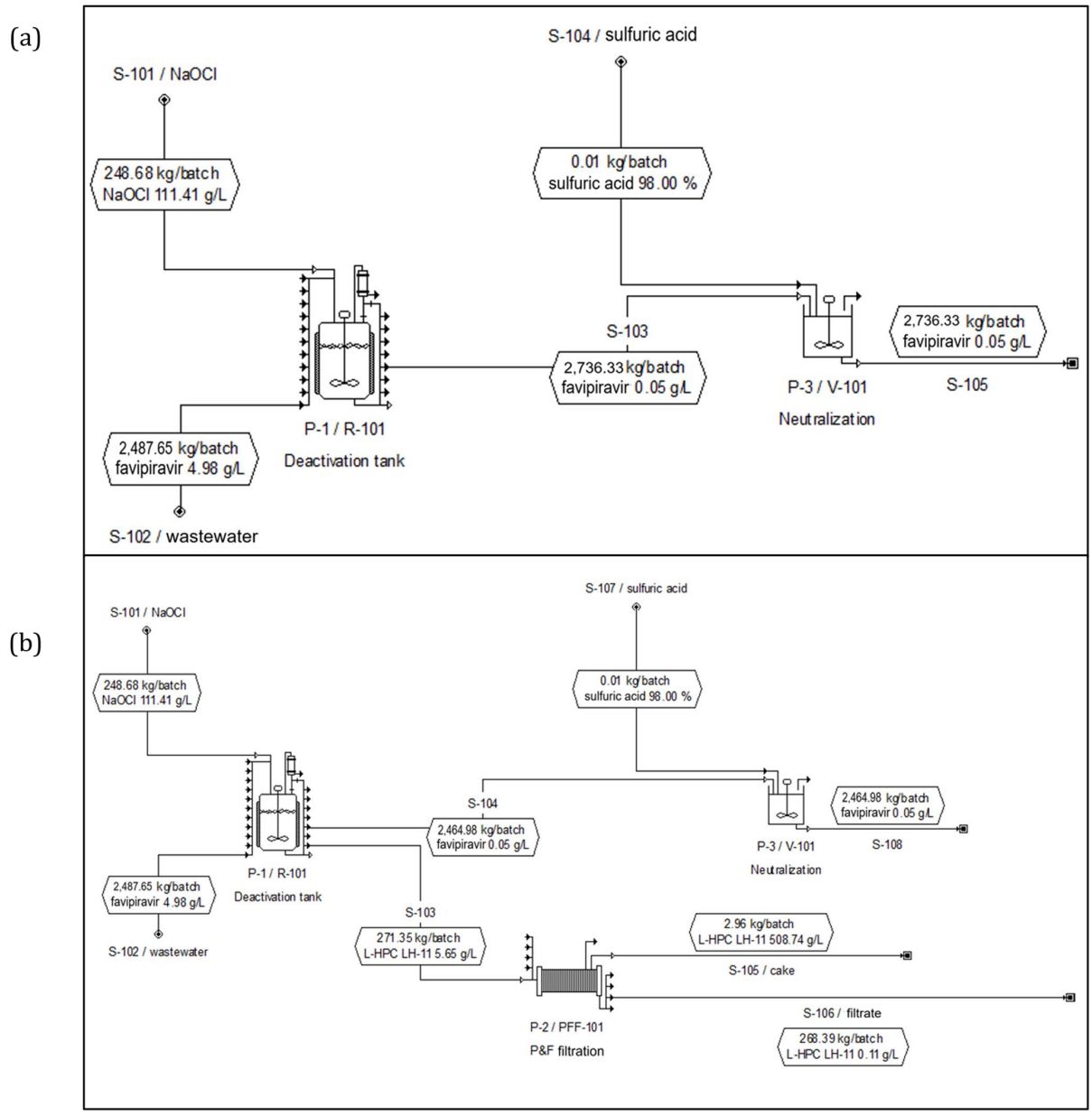

Figure 2. Overall process of FPV deactivation using NaOCl in (a) case IA without filtration and (b) case IB with the filtration unit

3.1.3 Neutralization unit

The FPV wastewaters deactivated by 2,736 kg per batch (S-103, case IA), and 2,465 kg per batch (S-104, case IB) of NaOCl were neutralized using a 4–m^3 neutralization tank (P-3/V-101), illustrated in Figures 2a and 2b, respectively. The neutralization time was set at 30 min. When the wastewater containing FPV was deactivated with NaOCl, the final pH of the mixture was approximately 10.7 (per our experiment). Thus, 0.01 kg per batch of 98% H_2SO_4 (S-107) was added to neutralize the pH of the mixture, allowing a suitable pH range for further treatment in the activated sludge unit. Adjusting the pH to a neutral value might have affected the solubility of the organic compounds contaminated in the wastewater (Lochyński et al., 2021); however, no significant impact was assumed for the pH adjustment in this study.

Figures 3a and 3b show that the neutralization tank (P-5/V-101) received 2,489 kg per batch without filtration, and 2,240 kg per batch with filtration of O_3-deactivated FPV wastewaters, respectively. Both of these are somewhat lower than the output of the NaOCl-treated wastewaters presented in case I. As FPV wastewater is acidic and adding O_3 does not change the pH, 50% NaOH at 0.08 kg per batch was used as a neutralizing agent in cases IIA and B. Theoretically, the effluents of the neutralization tanks in all cases are transferred to the activated sludge unit, which is beyond the scope of our study.

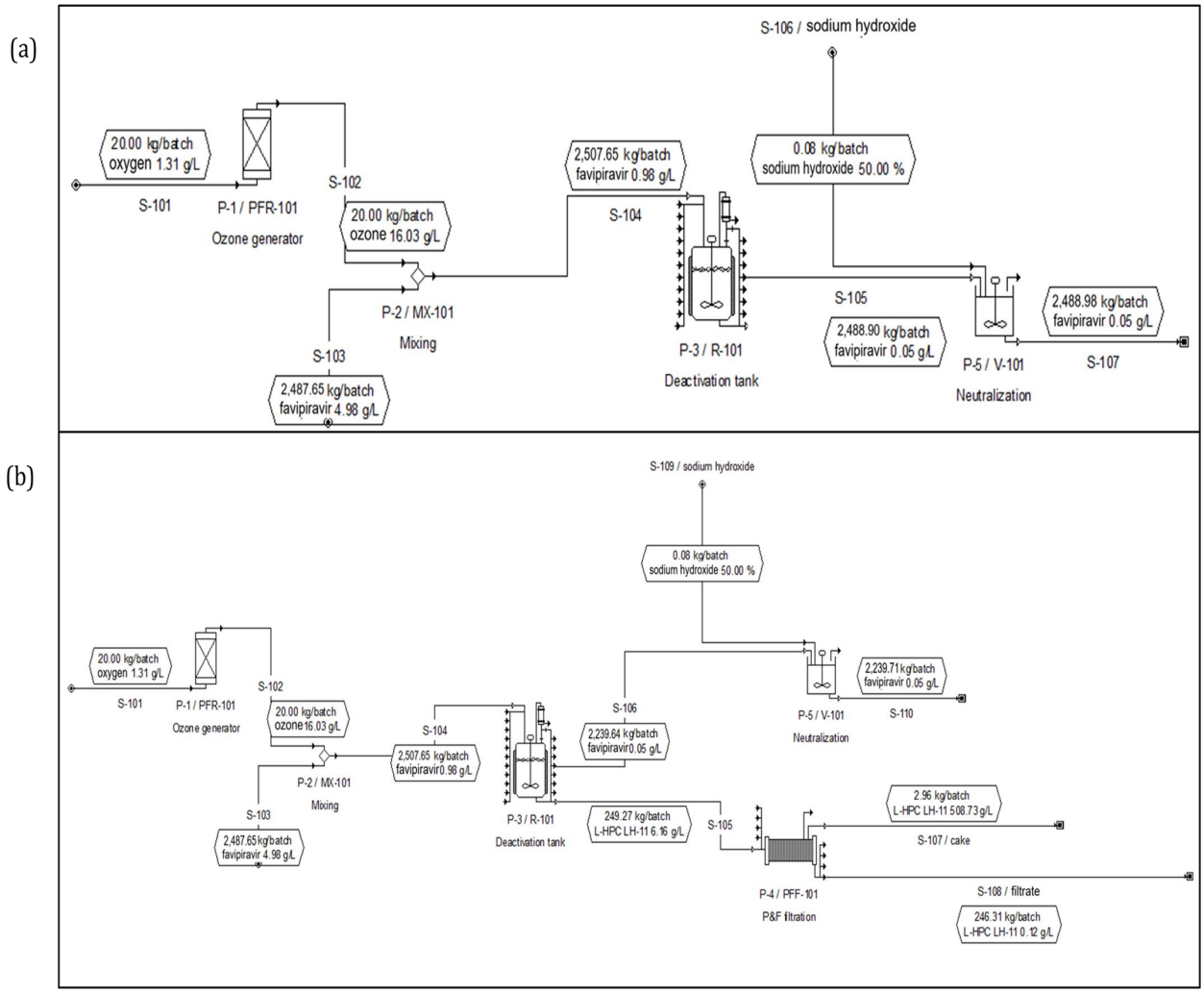

Figure 3. Overall process of FPV deactivation using O_3 in (a) case IIA without filtration and (b) case IIB with the filtration unit

The overall process simulation data for all cases are shown in Table 1, presenting the annual deactivation time and number of batches per year. It can be seen that the cases without the filtration unit (case IA and case IIA) provide more batches per year than the cases using the filtration unit. With the filtration process, the recipe batch time and cycle time are longer than those without filtration, resulting in a smaller number of batches per year. The number of batches per year indicates the ability to deactivate the FPV contaminating the wastewater. A greater number of batches per year is associated with greater FPV deactivation capability. From Table 1, without the filtration unit, case IA and case IIA can deactivate up to 3,959 and 5,279 batches per year of FPV in wastewater, corresponding to 49,243 and 65,661 kg of FPV per year, respectively.

Table 1. Overall process simulation data for the FPV deactivation process in all cases

Case	Recipe batch time (h)	Recipe cycle time (h)	Annual operating time (h)	Number of batches per year
Case IA	2.50	2.00	7,918.5	3,959
Case IB	3.00	2.50	7,918.1	3,167
Case IIA	2.00	1.50	7,919.0	5,279
Case IIB	2.50	2.00	7,918.5	3,959

Note: Recipe batch time is the duration it takes to complete one batch, starting from the initial cycle of the first operation to the final cycle of the last operation; recipe cycle time is the time between the start of two consecutive batches.

3.2 Cost estimation

SuperPro Designer performs a thorough cost analysis to estimate the capital costs (CAPEX) and operating costs (OPEX). Table 2 shows the total capital investment and operating costs of both the case I and case II scenarios. This total capital investment includes but is not limited to equipment purchase and installation costs, wastewater plant construction cost, startup and validation costs, and the working capital required for each project. The wastewater plant construction costs, such as the cost of buildings and piping, are estimated through multipliers in SuperPro Designer. The annual operating cost of the FPV deactivation process is related to the demand for a variety of resources (e.g., raw materials, consumables, labor, heating/cooling, and utilities) as well as additional operational costs (e.g., waste treatment/disposal cost, laboratory/QC/QA cost, facility-dependent cost, and miscellaneous costs).

Table 2. Cost summary of the FPV deactivation process in all scenarios

Case	Case IA	Case IB	Case IIA	Case IIB
CAPEX (USD)	117,000	192,000	821,000	873,000
Equipment	17,000	29,000	111,000	123,000
Installation	5,000	11,000	52,000	58,000
Process piping	6,000	10,000	39,000	43,000
Instrumentation	7,000	12,000	44,000	49,000
Insulation	1,000	1,000	3,000	4,000
Electrical	2,000	3,000	11,000	12,000
Buildings	8,000	13,000	50,000	55,000
Yard improvement	3,000	4,000	17,000	18,000
Auxiliary facilities	7,000	12,000	44,000	49,000
Engineering	14,000	24,000	93,000	103,000
Construction	19,000	33,000	130,000	144,000
Contractor's fee	4,000	8,000	30,000	33,000
Contingency	9,000	15,000	60,000	66,000
OPEX (USD)	138,400	144,300	1,259,600	1,010,400
Raw materials	83,000	66,000	1,108,000	831,000
Labor-dependent	31,000	38,000	19,000	31,000
Facility-dependent	19,000	33,000	129,000	142,000
Laboratory/QC/QA	5,000	6,000	3,000	5,000
Waste treatment/disposal	0	1,000	0	1,000
Utilities	374	272	511	353

Note: Facility-dependent cost (FDC) = maintenance + depreciation + miscellaneous costs
Labor-dependent cost (LDC) = $\sum[(LD_{operator} \times LR_{operator}) + (LD_{supervisor} \times LR_{supervisor})$
where LD is labor demand and LR is labor rate.
Utility cost is the total cost of heating/cooling utilities (e.g., heat transfer agents) and power utilized in a process

As expected, incorporating the filtration unit into the FPV deactivation process resulted in a higher total capital investment, as shown in Table 2. The operating cost of case IIA, even without filtration, was 1.25 times higher than that of case IIB, as more batches were performed in case IIA (Table 1). Adding an O_3 generator to the FPV deactivation process (without filtration) increased the total capital cost and operating cost 7-fold and 9-fold, respectively, compared to the NaOCl system. The operating cost per batch per year of case IIA is 238.6 US dollars (USD), which is 7 times higher than that of case IA (35.0 USD). Assuming one batch corresponds to 2.5 m^3, the operation cost of FPV deactivation could be as low as 13.96 USD/m^3 under the IA scenario. Kermet-Said and Moulai-Mostefa (2015) estimated the operating cost of the treatment of pharmaceutical wastewater by electrocoagulation to be 0.1053–2.8289 USD/m^3, depending on the electrolysis current densities and times. Our operating cost estimation was higher than that of the aforementioned report probably because the operating costs for both large-scale deactivation and neutralization tanks were considered, which require much more energy to operate. However, chemical treatment methods such as using NaOCl or O_3 can be highly efficient and require minimal energy input to achieve the desired

outcomes. Meanwhile, electrocoagulation involves the use of electrical energy to generate coagulant ions, which can be energy-intensive, particularly when dealing with large volumes of wastewater. Chemical treatment processes often involve fewer and less complex pieces of equipment than with electrocoagulation systems, which may include complex electrode arrays and power supplies. Chemical treatments can be easily scaled up or down to accommodate different wastewater treatment volumes without significantly increasing the energy consumption. In contrast, electrocoagulation may require more energy as the scale of the operation is increased. The OPEX analysis revealed that the highest contribution to operating expenses is the cost of raw materials. To address this issue, implementing efficient recycling practices and optimizing production processes are recommended to minimize waste and reduce material consumption. Additionally, the exploration of innovative, cost-effective sources of raw materials is necessary for the future. By implementing a combination of these strategies, it would be possible to reduce raw material costs while maintaining process efficiency.

4. CONCLUSION

This study probed several options for the treatment of wastewater containing antiviral drugs. O_3 deactivation (case IIA) demonstrated a higher deactivation capacity of 65,661 kg FPV (in wastewater) per year compared to 49,243 kg FPV per year for NaOCl deactivation (case IA). However, the total capital investment and operating costs for case IIA are significantly higher than those for case IA, indicating a tradeoff between deactivation capacity and costs. This is the first time, to our knowledge, that the design and simulation of the FPV deactivation process has been reported.

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REFERENCES

Antoniou, M. G., Hey, G., Vega, S. R., Spiliotopoulou, A., Fick, J., Tysklind, M., Jansen, J. L. C., and Andersen, H. R. (2013). Required ozone doses for removing pharmaceuticals from wastewater effluents. *Science of the Total Environment*, 456–457, 42–49.

Azuma, T., Ishida, M., Hisamatsu, K., Yunoki, A., Otomo, K., Kunitou, M., Shimizu, M., Hosomaru, K., Mikata, S., and Mino, Y. (2017). Fate of new three anti-influenza drugs and one prodrug in the water environment. *Chemosphere*, 169, 550–557.

Azuma, T., Nakada, N., Yamashita, N., and Tanaka, H. (2013). Mass balance of anti-influenza drugs discharged into the Yodo River system, Japan, under an influenza outbreak. *Chemosphere*, 93(9), 1672–1677.

Chayliem, J. (2018). *Treatment of hospital effluent using ozonation process for water recycle* [Master's thesis, Prince of Songkla University]. PSU Phuket Campus Library. https://opac.phuket.psu.ac.th/BibDetail.aspx?bibno=61270 [in Thai]

Chitniratna, K., and Peungsangarunchai, T. (2021). *Development of deactivation plant for favipiravir in pharmaceutical manufacturing facilities* [Unpublished undergraduate thesis]. King Mongkut's University of Technology Thonburi.

Huber, M. M., Canonica, S., Park, G.-Y., and von Gunten, U. (2003). Oxidation of pharmaceuticals during ozonation and advanced oxidation processes. *Environmental Science & Technology*, 37(5), 1016–1024.

Hussain, M., Mahtab, M. S., and Farooqi, I. H. (2020). The applications of ozone-based advanced oxidation processes for wastewater treatment: A review. *Advances in Environmental Research*, 9(3), 191–214.

Jarnerud, T., Karasev, A. V., and Jönsson, P. G. (2021). Neutralization of acidic wastewater from a steel plant by using CaO-containing waste materials from pulp and paper industries. *Materials*, 14(10), 2653.

Jin, Z., Smith, L. K., Rajwanshi, V. K., Kim, B., and Deval, J. (2013). The ambiguous base-pairing and high substrate efficiency of T-705 (favipiravir) ribofuranosyl 5′-triphosphate towards influenza A virus polymerase. *PLoS ONE*, 8(7), e68347.

Kermet-Said, H., and Moulai-Mostefa, N. (2015). Optimization of turbidity and COD removal from pharmaceutical wastewater by electrocoagulation. Isotherm modeling and cost analysis. *Polish Journal of Environmental Studies*, 24(3), 1049–1061.

Ki, D., Kang, S. Y., and Park, K.-M. (2021). Upcycling of wastewater sludge incineration ash as a 3D printing technology resource. *Frontiers in Sustainability*, 2, 697265.

Lochyński, P., Wiercik, P., Charazińska, S., and Ostrowski, M. (2021). Research on neutralization of wastewater from pickling and electropolishing processes. *Archives of Environmental Protection*, 47(4), 18–29.

Manabe, T., Kambayashi, D., Akatsu, H., and Kudo, K. (2021). Favipiravir for the treatment of patients with COVID-19: A systematic review and meta-analysis. *BMC Infectious Diseases*, 21(1), 489.

Morales-Paredes, C. A., Rodríguez-Díaz, J. M., and Boluda-Botella, N. (2022). Pharmaceutical compounds used in the COVID-19 pandemic: A review of their presence in water and treatment techniques for their elimination. *Science of the Total Environment*, 814, 152691.

Nippes, R. P., Macruz, P. D., da Silva, G. N., and Scaliante, M. H. N. O. (2021). A critical review on environmental presence of pharmaceutical drugs tested for the covid-19 treatment. *Process Safety and Environmental Protection*, 152, 568–582.

Piemont, A., Coatalem, A., Hinaut, B., Quintela, C., Cazaban, C., Delporte, C., Prevot, C., Gorski, D., Perrin, D., de Jong, E., Sutton-Sharp, E., Toledo, E., Judenne, E., Fenoglio, F., Perrin, F. P., Flores, G., Vanderghote, G., Gorisse, H., Perez, J., … Camy, V. (2021). *Liquid Sludge Treatment*. [Online URL: https://www.suezwaterhandbook.com/processes-and-technologies/liquid-sludge-treatment] accessed on January 28, 2023.

Singh, R. L., and Singh, R. P. (Eds.). (2019). Introduction. In *Advances in Biological Treatment of Industrial Waste*

Water and Their Recycling for a Sustainable Future, pp. 1–11. Singapore: Springer.

Tulbah, A. S., and Lee, W.-H. (2021). Physicochemical characteristics and in vitro toxicity/anti-sars-cov-2 activity of favipiravir solid lipid nanoparticles. *Pharmaceuticals*, 14(10), 1059.

Vogna, D., Marotta, R., Napolitano, A., Andreozzi, R., and d'Ischia, M. (2004). Advanced oxidation of the pharmaceutical drug diclofenac with UV/H_2O_2 and ozone. *Water Research*, 38(2), 414–422.

Wang, Z. (Ed.). (2010). Heumann indig process. In *Comprehensive Organic Name Reactions and Reagents*, pp. 1399–1402. Hoboken, NY: John Wiley & Sons.

Zhang, X., Ye, P., and Wu, Y. (2022). Enhanced technology for sewage sludge advanced dewatering from an engineering practice perspective: A review. *Journal of Environmental Management*, 321, 115938.